unit of said antisense oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage within said antisense oligonucleotide is not a phosphodiester or a phosphorothioate linkage.

REMARKS

Claims 37-59, 61, 63 and 64 are pending. Claims 38 and 50 have been canceled, without prejudice. Claims 37, 52-54, 59 and 61 have been amended. No new matter has been added. Support for the amendments can be found in the claims as originally filed. After entry of the amendment, claims 37, 39-49, 61, 63 and 64 will be pending.

As a preliminary matter, Applicants wish to thank the Examiner for the courtesy afforded Applicants' undersigned attorney and Mr. Bartfeld in an interview held on March 20, 2001, in which several issues were discussed and clarified.

During the interview, Applicants provided to the Examiner a Communication with a copy of references CW, DN, EJ, GI, GM, HM-HO, ID AND LF-LP. Applicants stated in the PTO Form 1449 mailed on September 13, 1999, that reference AA was too voluminous to submit.[1] The following U.S. Application Serial Numbers have been considered by the Examiner: Reference LF 08/383,666; LH 08/465,880; LI 08/468,037; LL 09/009,490; LN 09/044,506; LP

[1] The Office Action indicates that the IDS has been placed in the file, but the information in regard to reference "DC (Agrawal et al.) has not been considered". Applicants note that reference DC is not that of Agrawal et al., but of Staunton et al. and has been initialed.

09/071,433.[2] The Examiner agreed to send an initialed copy of the PTO Form 1449 with the next communication

Claims 38 and 50 are objected to as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. In an attempt to facilitate prosecution, Applicants have canceled these claims, thereby rendering the rejection moot.

Claims 37-59, 61, 63 and 64 stand provisionally rejected under 35 U.S.C. § 101 as allegedly claiming the same invention as copending application serial numbers 09/083,586 and 09/083,585. Applicants respectfully request reconsideration and withdrawal of the rejections as each application has been abandoned, thereby rendering the rejection moot. Claims 37-59, 61, 63 and 64 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over application serial no. 09/315,581. Applicants reiterate that given the provisional nature of the rejections, Applicants will address the rejections upon an indication of allowable subject matter in the instant application.

Claims 37-39, 61, 63 and 64 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter. Although applicants do not concur with the rejection, the claims have been amended in an attempt to advance prosecution. Applicants request that the rejections be withdrawn.

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[2] Applicants note that on page 3, the Office Action incorrectly refers to an IDS filed on December 6, 2000. In the present application, an IDS was filed on September 13, 1999 and a Supplemental IDS was filed March 29, 2000.

Rejections over Alleged Prior Art and Applicants' Claim for Priority

The present Office Action sets forth various rejections of the claims under 35 U.S.C. §§ 102 and 103. Applicants have amended the specification to claim priority under 35 U.S.C. §120 to U.S. application ser. no. 07/801,168, (hereinafter the 168 priority application) which was filed on November 20, 1991. Applicants also submit herewith a substitute declaration reflecting Applicants' claim of priority.

The claim for priority was discussed in the interview in connection with both the present application (hereinafter the 292 application), and in connection with copending application 09/315,581 (hereinafter the 581 application), which claims priority to the 168 application.[3] In the interview, it was explained to the Examiner that the disclosure provided on page 7 of the 168 priority application as originally filed, when combined with the level of skill of one of ordinary skill in the art at the time the 168 application was filed, provides sufficient support for the claim of priority in both the present application and in the copending 09/315,581 application. For example, page 7 of the 168 application provides that "oligonucleotides may be formulated in a pharmaceutical composition" which may then be "administered in a number of ways depending on whether local or systemic treatment is desired, and on the area to be treated." Among the methods disclosed is inhalation.[4]

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[3] The Examiner questioned the claim for priority in an Office Action issued in connection with the 09/315,581 application.

[4] It is believed that the Examiner has a copy of the priority document. If this is not the case, Applicants request that the Examiner contact Applicants' undersigned attorney, and a copy will be promptly provided.

Given the state of the art of pulmonary administration in 1991, one of ordinary skill in the art would have known how to administer the compounds of the 292 application according to the disclosure of the 168 application, which provides for administration by inhalation. The references submitted herewith exemplify the level of skill in the art at the time the 168 application was filed (November 20, 1991) and demonstrate that there were several well-known methods for pulmonary administration of many pharmaceutical compositions.

Aerosol therapy has been a form of drug delivery since the 19th century. *See* Cawley, "Aerosolized Administration of Drugs: Possible Future Agents and the Role of the RCP", *RTMagazine*, Feb. 1999, p.1-7. Introduction of a suspension of fine particles for respiration and treatment using a nebulizer has been known for approximately the last forty or fifty years. (*See* Clark, "Medical Aerosol Inhalers: Past, Present, and Future", *Aerosol Science and Technology*, 22:374-91 (1995), p. 375, col. 2). Knowledge of the use of dry powder inhalers and pressured metered dose inhalers (pMDI) can be traced back to the early to mid-1950's. (*See id.* at p. 375 & 382). In addition, the administration of many drugs (*e.g.* bronchodilators, albuterol, bitolterol, epinephrine, isoetharine, isoproterenol, metaproterenol, pirbuterol and terbutaline) using metered dose inhalers and nebulizers was well-known in the art in 1991. (See "How to Take Your Medicines: Adrenergic Bronchodilators (Inhaled), June 1991, **http://www.fda.gov/bbs/topics/CONSUMER/CON00005.html** p.2 last para. & p. 4).

Additional examples of the variety of compounds known to be aerosolized at the time of the filing of the priority application can be found in Kohler, "Aerosols for Systematic Treatment", *Lung* (1990) Suppl: 677-684. For example, Table 1 provides several different

categories of agents for pulmonary administration, including antibiotics and antiviral agents, immunosuppressive agents, antielastase, vaccines, surfactant, protease, antitumor agents, and anticold agents. (*See* p. 679). Copies of the above-identified references have been submitted herewith.

The discussion above underscores Applicants assertion that at the time of the filing of the priority application, the art pertaining to inhalation of therapeutics was well developed. Indeed, the cited references show that numerous compositions were being administered by inhalation, and various means were known for such administration. Thus, one of ordinary skill in the art at the time of the priority application would readily have appreciated how to administer oligonucleotide compounds by inhalation, once armed with the suggestion to do so provided by the priority application. Accordingly, Applicants' claim of priority to the 168 application is proper and should be acknowledged.

Claims 37, 38, 42, 44-59, 61 and 64 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,733,572 to Unger *et al.* ("Unger patent"). The Unger patent was filed on November 29, 1994, well after the date of the 168 priority application. Accordingly, the Unger patent is not available as prior art under 35 U.S.C. § 102(e).[5] Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

Claim 59 stands rejected under 35 U.S.C. § 102(b) in view of U.S. Patent No.

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[5] In the interview the Examiner kindly acknowledged that while the Unger patent on its face claims priority to various prior applications, including some that predate the filing date of the 168 priority document, establishment of Applicants' asserted priority date would remove the Unger applications as prior art.

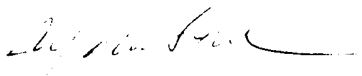
5,514,788 to Bennett *et al.* ("the Bennett patent"). For the reasons recited above, Applicants are entitled to an effective filing date of November 29, 1991. Accordingly, the Bennett patent, which issued on May 7, 1996, does not qualifies as prior art under 35 U.S.C. § 102(b), and cannot provide the basis for a rejection. Applicants therefore respectfully request withdrawal of the rejection.

Claim 61 stands rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by International Application No. WO 96/40266 to Nyce ("the Nyce reference"). However, as stated above, Applicants are entitled to an effective filing date of November 29, 1991. Therefore, the Nyce reference, which was published on December 19, 1996, does not qualify as prior art under 35 U.S.C. § 102(b). Applicants therefore respectfully request withdrawal of the rejection.

Claims 39-41, 43 and 63 stand rejected under 35 U.S.C. § 103(a) for alleged obviousness over the Unger patent, in view of Milligan, J.F, et al., J. Med. Chem. 1993, 36 (14) p. 1923-1937 (" the Milligan reference"); U.S. Patent No. 5,789,573 to Baker et al. ("Baker patent"); U.S. Patent No. 5,955,443 to Bennett *et al.* ("the Bennett patent"); U.S. Patent No. 5,948,898 to Dean et al. ("the Dean patent"); U.S. Patent No. 5,554,746 to Ravikumar et al., ("the Ravikumar patent") However, in view of the discussion above, the rejection has been rendered moot because the primary reference, the Unger patent, no longer qualifies as prior art. Therefore, the combination can no longer be made with the other references for purposes of the § 103(a) rejection. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Applicants respectfully submit that the claims presently before the Examiner patentably define the invention over the applied art and are otherwise in condition for ready allowance.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES

In the Specification

The first full paragraph on page 1 under the heading "Cross Reference to Related Applications (starting at line 4 and ending on line 7), was amended as follows:

[This application is a continuation-in-part of U.S. patent application serial no. 09/083,586 filed on May 21, 1998, the disclosure of which is incorporated by reference herein in its entirety.]

This application is a continuation-in-part of Serial No. 09/083,586, filed May 21, 1998 (abandoned), and is a continuation-in-part of Serial No. 09/083,585 filed on May 21, 1998 (abandoned), which is a continuation-in-part of Serial No. 07/794,396 filed on November 19, 1991, now U.S. Patent No. 6,034,233, and a continuation-in-part of Serial No. 08/227,180 filed on April 13, 1994, now U.S. Patent No. 5,866,698, which is a continuation-in-part of Serial No. 07/801,168 filed on November 29, 1991 (abandoned). The disclosures of each of the foregoing applications are hereby incorporated by reference in their entirety.

In the Claims

Claims 38 and 50 have been canceled. Claims 37, 52-54, 59 and 61 have been amended as follows:

37. (Once Amended) A method for the administration of an antisense nucleic acid therapeutic or diagnostic composition comprising:

aerosolizing an antisense nucleic acid therapeutic or diagnostic composition comprising at least one antisense oligonucleotide wherein the sugar moiety of at least one

nucleoside unit of said antisense oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage within said antisense oligonucleotide is not a phosphodiester or a phosphorothioate linkage [, wherein said antisense oligonucleotide is not directed to an A_1or A_3 adenosine receptor and is not contained in an expression vector] ; and

introducing the aerosolized antisense nucleic acid therapeutic or diagnostic composition into the lung of a mammal.

52. (Once Amended) A method of treating an animal having or suspected of having a disease or disorder that is treatable with an antisense nucleic acid composition comprising:

administering a therapeutically effective amount of an aerosolized antisense nucleic acid composition to the lung of the animal;

wherein the aerosolized antisense nucleic acid composition comprises at least one antisense oligonucleotide;

wherein the sugar moiety of at least one nucleoside unit of said antisense oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage within said antisense oligonucleotide is not a phosphodiester or a phosphorothioate linkage[;

wherein said antisense oligonucleotide is not directed to an A_1or A_3 adenosine receptor and is not contained in an expression vector].

53. (Once Amended) A method of investigating the role of a gene or gene product in an animal other than a human comprising:

administering a therapeutically effective amount of an aerosolized antisense nucleic acid composition to the lung of the animal;

wherein the aerosolized antisense nucleic acid composition comprises at least one antisense oligonucleotide;

wherein the sugar moiety of at least one nucleoside unit of said antisense oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage within said antisense oligonucleotide is not a phosphodiester or a phosphorothioate linkage[;

wherein said antisense oligonucleotide is not directed to an A_1or A_3 adenosine receptor and is not contained in an expression vector].

54. (Once Amended) A method for delivering an antisense nucleic acid therapeutic or diagnostic compound to the lung of an animal comprising applying to said lung a pharmaceutical composition comprising at least one antisense oligonucleotide wherein the sugar moiety of at least nucleoside unit of said antisense oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage within said antisense oligonucleotide is not a phosphodiester or a phosphorothioate linkage[;

wherein said antisense oligonucleotide is not directed to an A_1or A_3 adenosine receptor and is not contained in an expression vector].

59. (Once Amended) A method of modulating the expression of a gene in an animal comprising administering to said animal an antisense nucleic acid comprising at least one antisense oligonucleotide wherein the sugar moiety of at least nucleoside unit of said antisense oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage within said antisense oligonucleotide is not a phosphodiester or a phosphorothioate linkage[, wherein said antisense oligonucleotide is not directed to an A_1or A_3 adenosine receptor and is not contained in an expression vector].

61. (Once Amended) A medical device for pulmonary delivery of an aerosol comprising an antisense nucleic acid composition for pulmonary delivery of an antisense oligonucleotide comprising at least one antisense oligonucleotide wherein the sugar moiety of at least nucleoside unit of said antisense oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety

or at least one internucleotide linkage within said antisense oligonucleotide is not a phosphodiester or a phosphorothioate linkage[, wherein said antisense oligonucleotide is not directed to an A_1or A_3 adenosine receptor and is not contained in an expression vector].